Enantiospecific Formal Total Synthesis of (+)-Fawcettimine

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ABSTRACT

The diastereospecific attack of the silyl enol ether on the activated cyclopropyl diester 27 generated the hydrindanone 28 with complete stereocontrol. Thermal decarbomethoxylation of 28 gave the monoester 29, a key intermediate in Heathcock’s synthesis, thereby completing a formal total synthesis of (+)-fawcettimine 1. The analogous cyclization of 33, the diastereomer of 27, afforded the diastereomeric diester 34, thereby demonstrating that the cyclization process is diastereospecific.

(+)-Fawcettimine 1 is a tetracyclic alkaloid belonging to the Lycopodium class of alkaloids and was isolated in 1959 by Burnell (Figure 1).1 It exists predominantly as the carbinolamine, and the first total synthesis by Heathcock and co-workers proved the stereochemistry at C4.2 Because of its challenging tetracyclic structure and postulated role as a biosynthetic precursor to additional members of the Lycopodium family, it has generated considerable synthetic interest.3 We now report the enantiospecific formal total synthesis of (+)-fawcettimine 1 intercepting the Heathcock ester intermediate 29.

Recently we reported4 the acid-promoted stepwise Mukaiyama—Michael addition of hindered silyloxy dienes 5 to hindered enones 4 to give the formal cycloadduct 7 via the initial Mukaiyama—Michael adduct 6 (Scheme 1). For (+)-fawcettimine, a similar double addition process was conceived, this time with the cyclopropyl silyl enol ether 8 and enone 9 to access the hydrindanone core 11 by a tandem Mukaiyama—Michael homo-Michael process via the intermediate 10 (Scheme 2). Donor—acceptor (DA) cyclopropanes,5 including cyclopropane-1,1-diester, are known to undergo a wide array of reactions that include [3 + 2] and [4 + 3] cycloadditions leading to a variety of heterocycles, radical ring-openings, nucleophilic ring-openings, and metal-mediated coupling reactions;6 however, an annulation of this

Figure 1

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type has not been previously reported to our knowledge. Only two references have cited the attack of silyl enol ethers on cyclopropane-1,1-diesters, but in both cases the reactions were intermolecular. Therefore, we decided to test the viability of this idea using a model system.

Thus, the known methyl ketone \( \text{12} \)\(^8\) was converted to the kinetic (and thermodynamic) TBS silyl enol ether \( \text{13} \) by treatment with TBSOTf and Hüning’s base (Scheme 3). Triflimide-mediated Mukaiyama–Michael addition\(^4\) of \( \text{13} \) to 2-methylcyclohexenone \( \text{14} \) gave the ketone \( \text{15} \) as a mixture of diastereomers. Warming the reaction mixture did not afford the cyclopropane ring-opened product but instead gave the silyl enol ether hydrolysis product \( \text{16} \). Various fluoride reagents and Lewis acids were screened, but none of the conditions gave the annulated product and, in most cases, gave only the product of hydrolysis. To increase the reactivity of the system, the ketone \( \text{15} \) was subjected to standard Wittig methenylation conditions to give the 1,1-disubstituted olefin \( \text{17} \) in 73% yield. Treatment of \( \text{17} \) with a catalytic amount (20 mol %) of \( \text{Sc(OTf)}_3 \) gave the desired hydrindanone product \( \text{18} \) in 71% yield as a single regioisomer. To our knowledge, this is the first example of an intramolecular attack of a silyl enol ether on a cyclopropane-1,1-diester resulting in a new carbon–carbon bond to give an annulated product.

Encouraged by the results in the model system, we decided to demonstrate the utility of this method in a formal total synthesis of \((+)-\text{fawcettimine}\). Since only one regioisomer was obtained, we could safely rule out any “\( \text{S_N2}’ \)-like” or “\( \text{S_N1}’ \)-like” reaction mechanisms. Previous work\(^9\) done in this area on intermolecular cyclopropane-1,1-diester ring openings allowed us to postulate that the key ring-opening reaction occurred via a stereospecific \( \text{S_N2}’ \)-like mechanism as shown in Figure 2. Thus, Lewis acid complexation of one (or both) of the two esters of \( \text{A} \) would be followed by attack of the silyl enol ether on the activated allylic cyclopropyl-1,1-diester \( \text{B} \) without any loss of stereocontrol to give stereospecifically \( \text{C} \). To test this hypothesis, we decided to synthesize one diastereomer of the substrate and see if there were any loss of stereochemistry in the cyclized product.

After a simple molecular model analysis, it was determined that the previously unreported (\(\text{S}\))-methyl ketone \( \text{23} \) was

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\(\text{Figure 2}\)

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required to intercept Heathcock’s intermediate 29 for the formal synthesis of fawcettimine 1. Thus, the known bicyclic lactam 19 was treated sequentially with sodium hexamethyldisilazide, methyl chloroformate, and phenylselenenyl bromide, followed by an oxidative workup to give the α,β-unsaturated amide 20 in 77% yield (Scheme 4). Subjecting this very activated alkene 20 to standard Corey–Chaykovsky conditions gave the cyclopropane 21 as a single diastereomer. Hydrolysis of 21 in acidic methanol gave the methyl ketone 22 which was identical in all respects to the known (R) enantiomer, except for optical rotation. Finally, treatment of 22 with TBSOTf and Hüning’s base gave the desired kinetic TBS silyl enol ether 23.

The enone 25 required for the (+)-fawcettimine synthesis was obtained by Michael addition of the known sulfoxide 24 to acrylonitrile followed by thermal sulfoxide elimination in 51% yield (Scheme 5). The enone 25 and the silyl enol ether 23 were then treated with triflimide to give the corresponding ketone 26 as a single diastereomer (Scheme 6). Wittig methenylation of 26, though sluggish, afforded the desired olefin 27 in 75% yield (based on recovered starting material). To our delight, treatment of 27 with Sc(OTf)3 afforded cleanly the cyclopropane ring-opened product 28 in 77% yield as a single diastereomer. Thus this annulation had proceeded with complete stereocontrol in this system. To finish the formal total synthesis of 1, subjecting of 28 to modified Krapcho decarboxylation conditions gave, in 73% yield, the ester 29, which was identical in all respects to the ester previously reported by Heathcock, indicating that our molecular modeling prediction was correct.

Even though the Lewis acid-promoted intramolecular ring-opening cyclization of 27 to give 28 had proceeded with complete stereocontrol, we could not guarantee that this result was not due to a “matched” diastereoselective process or to kinetic control rather than a truly diastereospecific process. Therefore, to prove that the observed stereospecificity of the cyclization was not attributed to the intrinsic diastereoselectivity of the substrate, we decided to prepare the epimeric cyclopropane 31 to synthesize the C4 epimer (fawcettimine numbering). Thus, the known (R) methyl ketone 30 was synthesized according to the procedure of Meyers and then treated with TBSOTf and Hüning’s base to give the corresponding kinetic (R) silyl enol ether 31 (Scheme 7). Triflimide-mediated Mukaiyama–Michael addition of the silyl enol ether 31 to the enone 25 afforded the ketone 32. Wittig methenylation gave in 70% yield (brsm) the olefin 33, which on treatment with Sc(OTf)3 afforded 34 as a single diastereomer. Comparison of the spectroscopic data clearly indicated that 34 was not identical to the previously prepared malonate 28 and thus the ring opening was completely diastereospecific. Although we have not carried this compound forward, it is possible that compound 34 could still be a viable intermediate toward the synthesis of (+)-fawcettimine 1 based on the previous Heathcock synthesis.

In summary, we have shown that the process of a stepwise Mukaiyama–Michael addition of the silyl enol ether of an

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acetylcyclopropane-1,1-dicarboxylate, Wittig olefination, and final Lewis-acid-promoted cyclopropane opening affords hydridanones in good yield and with complete diastereoselection. Furthermore, we have shown that this process proceeds via an “SN2-like” mechanism (Figure 2) and is therefore completely diastereosepecific with full retention of the stereochemistry of the cyclopropyl center. Lastly, we have completed a formal total synthesis of (+)-fawcettimine 1.

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**Supporting Information Available:** Experimental procedures and proton and carbon NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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